SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Absorbable Hemostatic Agent
Device Trade Name:	Vitagel™ Surgical Hemostat
Applicant's Name and Address:	Orthovita, Inc. 45 Great Valley Parkway Malvern, PA 19355
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P050044
Date of Notice of Approval to Applicant:	June 16, 2006

II. INDICATIONS FOR USE

Vitagel™ Surgical Hemostat (hereinafter referred to only as Vitagel) is indicated in surgical procedures (other than in neurosurgical and ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

III. CDRH DECISION

This application includes by reference the data in PMA P990030 and related supplements for CoStasis® Surgical Hemostat submitted by Angiotech Biomaterials Corporation (formerly Cohesion Technologies, Inc.) and approved on June 13, 2000. Angiotech Biomaterials Corporation has given Orthovita, Inc. a license right to incorporate by reference the information contained in its approved PMA and related supplements.

The applicant's manufacturing facility was inspected and found to be in compliance with the Quality System Regulation (21 CFR 820). CDRH issued the approval order to Orthovita, Inc. on June 16, 2006.

For data supporting the approval decision refer to the attached summary of safety and effectiveness data for P990030.

IV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION:

DEVICE GENERIC NAME: Absorbable Hemostatic Agent

DEVICE TRADE NAME: CoStasis® Surgical Hemostat
DynaStat™ Surgical Hemostat

APPLICANT NAME AND ADDRESS: Cohesion Technologies, Inc.
2500 Faber Place
Palo Alto, CA 94303 USA

DATE OF PANEL RECOMMENDATION: None

PMA NUMBER: P990030

DATE OF GMP INSPECTION: November 3, 1999

DATE OF NOTICE OF APPROVAL TO APPLICANT: June 13, 2000

II. INDICATIONS FOR USE:

CoStasis® (also known as DynaStat™) Surgical Hemostat (hereafter referred to only as CoStasis in this Summary of Safety and Effectiveness) is indicated in surgical procedures (other than in neurosurgical, ophthalmic, and urological) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

III. CONTRAINDICATIONS:

- Do not inject CoStasis® Surgical Hemostat into blood vessels or allow it to enter blood vessels. Extensive intravascular clotting and even death may result.
- Do not use CoStasis® Surgical Hemostat in patients with known allergies to materials of bovine origin.

See Contraindications in the Package Insert for Thrombin-JMI® enclosed in the CoStasis package.

IV. WARNINGS AND PRECAUTIONS:

The warnings and precautions can be found in the CoStasis® Surgical Hemostat labeling.

V. DEVICE DESCRIPTION:

A. COSTASIS SYRINGE:

The CoStasis syringe contains a suspension of 20 mg/ml bovine collagen and at least 300 U/ml bovine thrombin in a 40 mM $CaCl_2$ buffer that is filled aseptically. After fill, the CoStasis syringe is sealed with a sterile barrier Luer closure and sealed inside a ported pouch. The ported pouch maintains the sterility of the surface of the syringe to allow placement into the sterile operating field. CoStasis is supplied in a fill volume of 5 ml for convenience of use. The CoStasis syringe is single use and is stored at refrigerated temperature.

B. TRANSFER SYRINGE IN PORTED POUCH:

The transfer syringe is made from radiation stable plastics meeting USP Class VI requirements. The transfer syringe is sealed in a ported pouch with closure and is then radiation sterilized. Patient plasma is aseptically transferred from the CellPaker to the sterile transfer syringe. After plasma transfer, the pouch is opened and the transfer syringe is removed and placed into the sterile operating field. The transfer syringe is single use and holds 5 ml of plasma.

C. DELIVERY SYSTEM:

The delivery system is provided to combine and mix the contents of the CoStasis syringe with the patient's plasma syringe at the time of administration to the bleeding site. The CoStasis delivery system is comprised of:

- A joiner to connect the CoStasis syringe to the syringe containing the patient's own plasma;
- A spray head incorporating a mixer element;
- A cannula incorporating a mixer element (provided as an alternate delivery component to the spray head);
- A syringe clip to permit the depression of the plunger rods of the two syringes simultaneously; and
- A syringe support to aid the surgeon in holding the assembled device.

In the event of clogging or accidental contamination during use, an additional mixer/spray head and mixer/cannula are provided. The delivery system parts are single use, sterile, and are made from radiation stable plastics meeting USP Class VI requirements. The parts are sealed in a tray within a tray and are then radiation sterilized. The surgical assistants assemble the delivery system in the operating room. Total time for assembly is less than five minutes. A description of the

assembly procedure for the delivery system with the CoStasis syringe and autologous plasma syringe is provided in the CoStasis Directions for Use.

D. CELLPAKER PLASMA COLLECTION DEVICE:

The CellPaker contains sodium citrate and is used to collect and anticoagulate the patient's blood. After blood collection, the CellPaker is placed into a centrifuge to separate the plasma from cells. The CellPaker is made from radiation stable plastic meeting USP Class VI requirements, and is radiation sterilized prior to aseptic filling with sodium citrate. The CellPaker containing sodium citrate is single use and is stored at room temperature.

The procedure for obtaining autologous plasma is described in the Directions for Use provided with the CellPaker. For convenience and economy of use, the CellPaker is provided in single or multiple unit boxes.

VI. ALTERNATIVE PRACTICES OR PROCEDURES:

Intra-operative hemostasis may be accomplished by a variety of methods including occlusive procedures (e.g., direct pressure, suture, etc.), electrocautery, lasers, fibrin sealants, and the use of thrombin and absorbable hemostatic agents. The absorbable hemostatic agents consist of porcine gelatin powder and sponges, bovine gelatin matrix, bovine collagen sheets and sponges and oxidized cellulose sponges. Bovine thrombin is also used for hemostasis, but it often used in conjunction with gelatin or collagen hemostatic agents. Thrombin may not be used with oxidized cellulose, since the acidity of the cellulose inactivates the thrombin.

VII. MARKETING HISTORY:

CoStasis is CE Marked and was introduced into commercial distribution in Europe in January 1999, however, CoStasis has not been marketed in the United States. The CoStasis Surgical Hemostat has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

In a randomized prospective, concurrently controlled clinical trial, 318 patients were treated with CoStasis or the Control (a collagen absorbable hemostat for the non-cardiac procedures, and other conventional methods selected by the surgeon for cardiac procedures). The most common adverse events recorded during and after the application of the hemostatic agents were fever, pain, nausea, and atelectasis. Table 1 is a complete list of adverse events reported in greater than 5% of CoStasis treated patients that were observed in the clinical trial. The corresponding adverse events for the Control group are listed for comparison. None of the adverse events listed in the table were determined to be attributed to CoStasis.

Table 1: A Summary of Adverse Events Occurring in Greater Than 1% of the Study Patients.

Adverse Events Reported in Greater than 5% of Patients in CoStasis Clinical Trial Patients		
Adverse Event	CoStasis	Control* (absorbable collagen hemostat)
Fever	51 (30.4%)	41 (27.3%)
Pain	38 (22.6%)	33 (22.0%)
Nausea	34 (20.2%)	29 (19.3%)
Atelectasis	32 (19.0%)	27 (18.0%)
Pleural Effusion	24 (14.3%)	28 (18.7%)
Anemia	23 (13.7%)	27 (18.0%)
Peripheral Edema	19 (11.3%)	11 (7.3%)
Tachycardia	16 (9.5%)	20 (13.3%)
Constipation	14 (8.3%)	9 (6.0%)
Rash	14 (8.3%)	15 (10.0%)
Infection	13 (7.7%)	13 (8.7%)
Abnormal Healing	12 (7.1%)	12 (8.0%)
Abdominal Pain	11 (6.5%)	15 (10.0%)
Edema	11 (6.5%)	7 (4.7%)
Lung Disorder	11 (6.5%)	11 (7.3%)
Pericarditis	10 (6.0%)	13 (8.7%)
Nausea/Vomiting	10 (6.0%)	8 (5.3%)
Lung Edema	9 (5.4%)	9 (6.0%)
Pneumonia	9 (5.4%)	9 (6.0%)
Pruritis	9 (5.4%)	12 (8.0%)

***For the cardiac group, the control was selected by the surgeon, based on his/her conventional methods, including absorbable collagen hemostats, surgical tamponade, electrocautery with or without tamponade, gelatin sponge with thrombin, or no treatment.**

Other adverse events observed in less than 5% of the CoStasis treated clinical trial patients were bleeding, hypertension, hypotension, dyspnea, urinary tract infection, back pain, apnea, abscess, allergic reaction, death, chest pain, ecchymosis, hypokalemia, confusion, ileus, pharyngitis, ascites, asthenia, headache, atrial fibrillation, hypervolemia, dizziness, insomnia, paresthesia, increased coughing, oliguria, sepsis, arrhythmia, diarrhea, jaundice, hypomagnesemia, bone pain, anxiety, respiratory disorder, skin ulcer, hematuria, abnormal kidney function, fibrotic surgical wound, necrosis, pain at injection site, angina pectoris, heart arrest, heart failure, ventricular tachycardia, gastritis, GI disorder, melena, vomiting, leukocytosis, leukopenia, acidosis, bilirubinemia, hyperglycemia, hyponatremia, agitation, depression, hallucination, abnormal thinking, pneumothorax, sweating, kidney failure, breast pain, abdominal enlargement, cellulitis, chills, edema at injection site, hernia, anemia, cardiovascular disorder, extrasystoles, shock, syncope, superior ventricular tachycardia, anorexia, dyspepsia, GI bleeding, rectal

bleeding, abnormal liver function, oral monilia, increased coagulation time, thrombocytopenia, increased creatinine, cyanosis, hypoglycemia, hypophosphatemia, joint disorder, myasthenia, abnormal dreams, stupor, asthma, voice alteration, skin disorder, abnormal urination, vaginitis, asthesia, granuloma, hypothermia, injection site reaction, injury accident, neck rigidity, necrosis at injection site, overdose, sarcoma, seroma, thirst, vascular anomaly, sinus bradycardia, bundle branch block, cardiomegaly, pericardial effusion, ventricular extrasystoles, myocardial infarction, deep thrombophlebosis, thrombosis, thrombophlebosis, peripheral vascular disorder, varicose vein, anastomosis leak, liver carcinoma, colitis, eructation, dysphagia, tongue edema, fecal incontinence, liver failure, stomatitis, tooth disorder, agranulocytosis, hypovolemia, seroma, alkalosis, avitaminosis, dehydration, general edema, gout, hypocalcemia, arthrosis, myalgia, general spasm, aphasia, convulsions, hemiplegia, hypertonia, movement disorder, neuropathy, bronchiectasis, pulmonary embolism, emphysema, hemoptysis, hyperventillation, hypoxemia, hypoxia, infection, lung function decrease, rhinitis, vesiculobullous rash, bone pain, eye pain, breast carcinoma, epididymitis, impotence, urinary incontinence, metrorrhagia, nephrosis, urethral pain, testis disorder, urinary retention.

One adverse event was deemed by the surgeon to be related to the use of CoStasis: blocked inguinal drainage tube reported on day 11 post surgery. No other adverse events were deemed by the surgeon to be related to the use of CoStasis.

Fifteen (15) subjects died during the course of this study. Eleven died before the completion of the 8 week post-op visit and 4 died as of (or after) their final follow-up. None of the deaths were attributable to either CoStasis or the control, rather, it was determined that these patients died as a result of their underlying disease conditions or from unrelated postoperative surgical complications, e.g. respiratory insufficiency, sepsis and multi-organ failure. Nearly half (7 of the 15 deaths) were in the cardiac bypass group, 6 were among the general surgery subjects, and 2 in the hepatic group. Seven deaths occurred in CoStasis treated patients and 8 deaths were in the controls.

Reported Adverse Events Seen With other Absorbable Hemostatic Agents:

- Hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.

- Giant cell granulomas have been observed at implant sites when used in the brain.

- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid has been observed.

- Multiple neurologic events were reported when absorbable hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence.

- The use of absorbable hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations, has been associated with fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, impotence, and paresis.

- Foreign body reactions, "encapsulation" of fluid, and hematoma have been observed at implant sites.

- Toxic shock syndrome was reported in association with the use of absorbable hemostatic agents in nasal surgery.

- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

Adverse Reactions to Thrombin:

See Adverse Reactions in Package Insert for Thrombin-JMI® enclosed in the CoStasis™ Surgical Hemostat package.

IX. SUMMARY OF PRECLINICAL STUDIES:

There is an extensive history on the safe use of bovine collagen and bovine thrombin in humans. Therefore, standard biocompatibility tests as defined in the ISO 10993 standard were not conducted on CoStasis. Animal studies were done to evaluate the hemostatic performance of CoStasis in a variety of surgical wounds. Key studies and findings are summarized below.

A. SAFETY STUDIES:

Evaluation of Composite Tissue Adhesive (CoStasis Surgical Hemostat) as a Hemostat in a Diffuse Organ Bleeding Rabbit Survival Study.

The local biocompatibility of CoStasis was compared with fibrin sealant and Instat collagen sponge. Incisions of controlled dimensions were made in the kidneys of rabbits. The test materials were applied to the defect and animals were evaluated at 7, 14, 30, and 60 days post-operatively. Histologically, all materials demonstrated equivalent inflammation at 7 and 14 days post-operatively. Little to no CoStasis was observed in animals 14 days post-operatively. Instat was observed in animals at 30 days post-operatively, and fibrin sealant was observed in animals at up to 60 days post-operatively.

B. EFFECTIVENESS STUDIES:

Comparison of CoStasis Surgical Hemostat with Instat, Tisseel, and Fibrin Sealant Controls for Hemostatic Qualities in a Diffuse Bleeding Model in Parenchymal Organs of Rabbits.

The performance of CoStasis was compared to some other absorbable hemostatic products. These comparative products were a commercially available absorbable collagen sponge, a commercially available fibrin sealant and a non commercially available fibrin sealant. Incisions of controlled dimensions were made in the kidney and spleen of rabbits. The test materials were applied to the defect and time to hemostasis measured. The mean time to hemostasis was significantly faster using CoStasis as compared to the control materials. In spleen sites, CoStasis had a consistently faster time to hemostasis than all of the controls but only statistically significantly faster than the collagen pad and the non-commercially available fibrin sealant.

Effect of Variation in Platelet and Fibrinogen Levels in Plasma on Hemostatic Performance of CoStasis Surgical Hemostat.

This study evaluated the effect of plasma depleted of platelets and/or fibrinogen on the hemostatic performance of CoStasis. A rabbit model involving incisions of controlled dimensions in kidney and spleen was used. Time to hemostasis was measured. Plasma depleted of platelets or fibrinogen alone did not significantly affect the hemostatic performance of CoStasis. These formulations also had significantly faster times to hemostasis than the control collagen sponge. CoStasis with plasma depleted of platelets and fibrinogen resulted in a significantly slower time to hemostasis than CoStasis with plasma containing normal levels of platelets and fibrinogen.

Hemostatic Performance of CoStasis® Surgical Hemostat in Aspirin and Heparin Anticoagulated Rabbits.

CoStasis was compared to commercially available hemostatic agents (collagen sponge and fibrin sealant) in aspirin and heparin anticoagulated rabbits. A rabbit model involving incisions of controlled dimensions in kidney and spleen was used. Separate groups of rabbits were pretreated with one of two different medications known to impair hemostasis (aspirin and heparin). Impairment of hemostasis was confirmed by laboratory assessment of platelet activity. Mean time to hemostasis and total blood loss was measured. Comparison of CoStasis to an absorbable collagen sponge was done in aspirin treated animals. Comparison of CoStasis, an absorbable collagen sponge, and fibrin sealant was done in heparin treated animals. In all cases, the mean time to hemostasis was faster for CoStasis as compared to the control hemostats in aspirin or heparin treated animals. Blood loss was also significantly reduced in all animals treated with CoStasis.

Evaluation of CoStasis Surgical Hemostat for Hemostatic Qualities in an Ovine Parenchymal Organ Bleeding Model.

The hemostatic performance of CoStasis was compared to fibrin sealant in sheep. In addition, systemic anticoagulation conditions were evaluated using a high dose of heparin. Incisions of controlled dimensions were made in the kidneys, spleen,

and liver. The test materials were applied to the defect. Blood loss and time to hemostasis were recorded. In all surgical sites in normal or heparinized animals, CoStasis demonstrated faster mean times to hemostasis than fibrin sealant. Blood loss between the two groups was similar in normal animals. In heparinized animals, treatment with CoStasis resulted in significantly reduced blood loss when compared to treatment with fibrin sealant.

C. PRECLINICAL CONCLUSIONS:

These preclinical studies showed that CoStasis had a faster time to hemostasis than commercially available control materials (an absorbable collagen sponge and a fibrin sealant) and also a non-commercially available fibrin sealant. When the plasma component of CoStasis was depleted of either platelets or fibrinogen, the hemostatic performance of CoStasis remained. In addition, complete hemostasis using CoStasis was achieved in anticoagulated (aspirin or heparin treated) animals.

X. SUMMARY OF CLINICAL STUDIES:

The objective of the clinical studies was to assess the safety and effectiveness of the CoStasis™ Surgical Hemostat in the treatment of bleeding during surgical procedures. Three Studies were summarized in this PMA, a US feasibility study, an expanded European study and an expanded US study.

A. US FEASIBILITY STUDY:

A feasibility study was completed in the United States evaluating CoStasis in treating skin graft donor sites. Nine (9) patients were enrolled in this study.

Time to hemostasis using CoStasis was measured from the moment that the fresh wound was completely coated with the device. The clinical protocol used the terms *primary* and *secondary* hemostasis because it was anticipated that sites would pass through an oozing phase (primary hemostasis) before bleeding stopped completely (secondary hemostasis). Because the protocol did not allow reapplication of the device, the recorded times refer to observations made after a single application. In eight of the nine subjects, primary and secondary hemostasis times were identical. Primary hemostasis was achieved in a mean time under ten seconds. In one subject, the bleeding was controlled at seven seconds, while a small area of breakthrough bleeding continued to bleed for 142 seconds.

Adverse events were solicited at each visit; a total of 58 events were reported. Investigators assigned causality for all adverse events and no reported event was attributed to the investigational device. All reported events were classified as either related to the surgical procedure or unrelated. Healing of the harvested sites was considered normal with the exception of one patient who removed his own

dressing prematurely.

B. EXPANDED EUROPEAN STUDY:

The European study included treatment of 111 subjects in seven investigational centers in Germany and Austria. The primary effectiveness outcome was a comparison of the rate of failure to achieve hemostasis for CoStasis versus a commercially available fibrin sealant at the anastomotic site during coronary artery bypass grafting. Additional bleeding sites, beyond the primary anastomotic site, were evaluated and included the sternal edge (bone) and the chest wall capillary bed. Standard surgical practice in Europe uses a fibrin sealant only on the anastomotic site. Therefore, other methods and techniques, including cautery, tamponade, and bone wax were used as controls for the sternal edge and chest wall capillary bed.

For the primary performance endpoint of failure to achieve hemostasis on the anastomotic suture line, CoStasis was not different from the fibrin sealant (Fisher's Exact $p = 0.708$). In addition to this primary endpoint, analyses of times to hemostasis were conducted. The time to complete hemostasis (median $\pm$ 1 standard error) on the anastomotic site was nearly identical for CoStasis (52 $\pm$ 16 seconds) and the commercially available fibrin sealant (52 $\pm$ 6 seconds), Wilcoxon p-value = 0.68. When comparing median time to complete hemostasis for CoStasis versus the control along the sternal edge, CoStasis was faster (70 $\pm$ 14 seconds) than controls (136 $\pm$ 28 seconds), Wilcoxon p-value = 0.03. On the capillary beds, the median time to complete hemostasis were similar for CoStasis hemostat (60 $\pm$ 11 seconds) and control (120 $\pm$ 17 seconds), Wilcoxon p-value = 0.14.

C. EXPANDED US STUDY:

Study Design:

The US study was designed to evaluate the safety and effectiveness of CoStasis in hepatic, general, cardiac and orthopedic surgery. As a control, a collagen hemostatic sponge was used in the general, hepatic and orthopedic groups. A comparison of CoStasis to standard of care was used in the cardiac group.

Study Procedure:

The study was performed at 10 centers and randomized 347 subjects. Twenty-nine subjects were removed after randomization but before treatment, 14 CoStasis and 15 controls. A total of 318 patients advanced to treatment and became the intent to treat group. Of the 318 patients treated, 6 were eliminated from effectiveness analyses for various protocol violations leaving 312 evaluable patients. The patients treated in each surgical group are provided in Table 2.

Table 2: Surgical Groups

Surgical Group	# Treated
General Surgery	154
Cardiac Surgery	74
Hepatic Surgery	68
Iliac Crest Surgery	22
Total Patients Evaluated	318

The primary effectiveness outcome was a comparison of the success rate for each treatment group to achieve complete hemostasis (at 10 minutes for all groups except the cardiac group where it was at 3 minutes) for CoStasis versus control for each bleeding site. The statistical analysis used the Fisher's Exact test on the success rates to achieve hemostasis between treatments and controls. As CoStasis was being evaluated as a general hemostatic device, data from all surgical groups were pooled for statistical analysis. In addition to a comparison of the hemostasis success rates, discrete times to achieve hemostasis were compared using a Kaplan-Meier survival plot. Using this plot, the Logrank (Mantel-Cox) and Breslow-Gehan-Wilcoxon p-values were calculated.

This study was also designed to evaluate the safety of CoStasis. The safety evaluation included adverse events reported, clinical laboratory evaluations and an evaluation of antibovine and antihuman antibody titers to thrombin, collagen, and Factor V. Table 3 summarizes the patient accountability data for this clinical study.

Table 3: Patient Accountability Data

Accountability Category	CoStasis	Control	Total
Number Randomized	182	165	347
Number Treated	168	150	318
Number Evaluated for Effectiveness	166	146	312
Number Evaluated for Safety	168	150*	318

*One control patient was treated in two surgical groups. This patient was evaluated for safety in each group.

Study Results:

A total of 152 patients were treated in the general surgery group. The general surgery group was analyzed both as a whole group, and also in five subgroups that included, laparotomy (24 patients), retroperitoneal surgery (39 patients), muscle flaps (47 patients), breast/soft tissue (31 patients), and liver transplants (11 patients). The liver transplant patients were included in the general surgical group rather than the hepatic group as the bleeding site treated was the retroperitoneal bed and not the liver itself. A total of 67 patients were treated in the hepatic group. A total of 74 patients were treated in the cardiac group. Sixty-six (66) subjects in the cardiac group were evaluated for control of bleeding at the sternum, fifty-eight (58) for control of bleeding at the anastomotic sites, and thirty-six (36) for control of bleeding in the chest wall capillary bed. A total of 19 patients were treated in the iliac crest surgery group.

Table 4 analyzes the treatment sites achieving complete hemostasis within 10 minutes (intent to treat) for the various surgical groups using the 10-minute time limit for complete hemostasis.

Table 4: Treatment Sites Achieving Complete Hemostasis Within 10 Minutes Intent-to-Treat Sites (Success/Total)

Surgical Group	CoStasis	Control
All Treated Sites (non-cardiac group)	97% (126/130)	66% (75/114)
General	97% (77/79)	67% (50/75)
Hepatic	100% (39/39)	69% (20/29)
Iliac Crest	83% (10/12)	50% (5/10)

The treatment sites achieving complete hemostasis within 3 minutes in the cardiac group is given in Table 5. For the cardiac group each treatment site was timed for 3 minutes as the success time limit rather than the 10-minute limit used for the other surgical groups. For this analysis, intent to treat patients are presented.

Table 5: Treatment Sites Achieving Complete Hemostasis Within 3 Minutes Intent-to-Treat Sites (Success/Total)

Cardiac Group	CoStasis	Control*
All Treated Sites	93% (74/80)	55% (46/84)
Anastomotic	97% (28/29)	59% (17/29)
Sternal Edge	83% (25/30)	44% (15/34)
Capillary Bed	100% (21/21)	67% (14/21)

*For the cardiac group, the control was selected by the surgeon, based on his/her conventional methods, including absorbable collagen hemostats, surgical tamponade, electrocautery with or without tamponade, gelatin sponge with thrombin, or no treatment.

The study data for the number of treatment sites achieving complete hemostasis within the success criteria time limit (10 minutes for all surgical types except cardiac surgery and 3 minutes for cardiac surgery) were compared using two statistical tests. CoStasis and control were shown to be equivalent using the Blackwelder and Chang test, using a δ (clinically significant difference) of 0.25 ($p < 0.01$). For treatment sites achieving complete hemostasis, the difference

between CoStasis and control was also shown to be statistically significant using the Fisher's Exact test ($p < 0.05$), except for the Iliac Crest Group ($p = 0.17$).

Tables 6 shows the cumulative percent of treatment sites with complete hemostasis over the entire 10-minute study period for the combined general, hepatic and iliac crest patients and Table 7 shows the cumulative percent of treatment sites with complete hemostasis for the cardiac patients.

Table 6:
Cumulative Percent of Treatment Sites with Complete Hemostasis Over 10 Minutes Intent-to-Treat Sites for General, Hepatic, and Iliac Crest Groups (Success/Total)

Time Interval	CoStasis	Control
0 – 1 minute	37% (48/130)	4% (5/114)
1 – 2 minutes	60% (78/130)	17% (19/114)
2 – 3 minutes	75% (97/130)	27% (31/114)
3 – 6 minutes	94% (122/130)	50% (57/114)
6 – 10 minutes	97% (126/130)	66% (75/114)

Table 7:
Cumulative Percent of Treatment Sites with Complete Hemostasis Over 3 Minutes Intent-to-Treat Sites for Cardiac Group (Success/Total)

Time Interval	CoStasis	Control
0 – 1 minute	51% (41/80)	2% (2/84)
1 – 2 minutes	75% (60/80)	20% (17/84)
2 – 3 minutes	93% (74/80)	55% (46/84)

For the above analyses, hemostasis time was measured with a stopwatch at all treatment sites. Timing for subjects treated with CoStasis began as the spray made its first contact with the bleeding surfaces. Timing for control subjects began with the first application of the control collagen sponge. Times to complete hemostasis (median ± 1 standard error) for the intent to treat patients were also collected and are presented in Tables 8 and 9. The times to achieve complete hemostasis for all study groups were statistically different using the Breslow-Gehan-Wilcoxon test ($p < 0.05$).

Table 8: Times to Achieve Complete Hemostasis General, Hepatic and Iliac Crest Groups (Median ± 1 standard error) (Intent to Treat Patients)		
Surgical Group	CoStasis (seconds)	Control (seconds)
All Patients	90 ± 20	347 ± 27
General	65 ± 13	345 ± 63
Hepatic	150 ± 19	360 ± 52
Iliac Crest	90 ± 35	347 ± 343

Table 9: Time to Achieve Complete Hemostasis Cardiac Group (Median ± 1 standard error) (Intent to Treat Patients)		
Treatment Site	CoStasis (seconds)	Control (seconds)
All Treatment Sites	55 ± 4	180 ± 6
Sternal Edge	68 ± 33	> 180
Anastomosis	62 ± 12	180 ± 53
Capillary Bed	50 ± 5	180 ± 19

Additional measurements of effectiveness including transfusion requirements and tube drainage were similar between treated and control patients.

Serology Results:

Patients' sera were evaluated using an indirect enzyme-linked immunosorbent assay (ELISA). Sera samples obtained pre-surgery (Visit 1) and again at

approximately eight weeks (Visit 5) following surgery were tested for antibodies to bovine dermal collagen, bovine thrombin, and bovine Factor V/Va.

Of all the patients' sera tested, only 2 of the 172 pretreatment samples (~1%) were positive for any antibodies against bovine collagen, both were in the CoStasis group. At the eight week timepoint (visit 5), 8% of CoStasis treated patients had a positive antibovine collagen antibody titer. Of the control patients, 4% converted to a positive titer, all being in the collagen sponge group. None of the serum samples with equivocal or positive titers to bovine collagen showed any reactivity to human collagen type I or III.

Approximately 6% of all pretreatment sera were equivocal or positive for reactivity to bovine thrombin (6/172), equally divided between CoStasis and controls. One of these patients showed equivocal reactivity to human thrombin. At visit 5, positive antibody titers to bovine thrombin were found in 29% of sera from CoStasis treated patients. Twelve percent of the control patients had positive titers. Of the 27 CoStasis treated patients that had positive antibovine thrombin antibody titers, 30% (8/27) showed positive antihuman thrombin antibody titers. In the control group, of the 10 patients that had positive antibovine thrombin antibody titers, 10% (1/10) were positive antihuman thrombin antibody titers.

Three patients had reactivity to bovine Factor V in their pretreatment sera: two with equivocal titers and one positive. All of these patients were in the control group. A single CoStasis patient developed a positive antibovine Factor V antibody titer. This patient was also positive for antibovine thrombin antibodies at visit 5, but not positive for antihuman thrombin or antihuman Factor V antibodies. In the controls, one pretreatment patient with a positive titer remained positive. None of the samples with equivocal or positive titers to bovine Factor V showed any reactivity to human Factor V.

Clinical Laboratory Evaluations:

Clinical laboratory evaluations were undertaken pre-surgery and again post-surgery. No clinically significant findings were observed in the change-from-baseline laboratory tests for all treated patients.

XI. CONCLUSIONS DRAWN FROM THE STUDIES:

A. RISK BENEFIT ANALYSIS:

The absence of any significant adverse event related to product use, and the hemostatic effectiveness of CoStasis, attest to the acceptable risk/benefit ratio of CoStasis in controlling diffuse bleeding.

B. SAFETY:

The materials used to manufacture CoStasis are well defined with proven acceptable biocompatibility. The number of patients developing antibodies to bovine collagen, thrombin and Factor V were not different from that experienced in other applications of these materials, e.g. topical thrombin used in surgery and injectable collagen products for soft tissue augmentation. The absence of any significant adverse event related to use of CoStasis supports the safety of CoStasis for use in controlling diffuse bleeding.

C. EFFECTIVENESS:

The results of the preclinical and clinical testing demonstrated that there is reasonable assurance of safety and effectiveness for the CoStasis® Surgical Hemostat for the stated indication for use. The sponsor performed a randomized, parallel, controlled, comparative, multicenter clinical trial designed to determine the hemostatic ability of CoStasis in surgical patients. The general, hepatic and orthopedic surgery control groups were treated with a legally marketed absorbable collagen sponge while standard of care was used as the control for the cardiac surgery patients. The preclinical and clinical data support the hemostatic performance and safety of CoStasis when compared to the commercially available control treatments. CoStasis controlled bleeding in less time than the control treatments when time to hemostasis was compared. CoStasis was also observed to have a higher success rate than control when complete hemostasis was measured at 10 minutes for the general surgery, hepatic surgery and iliac crest surgery groups and at 3 minutes for the cardiac surgery group. Additional measurements of effectiveness including transfusion requirements and tube drainage were similar between treated and control patients.

XII. PANEL RECOMMENDATION:

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION:

A GMP inspection was conducted of the Cohesion Technologies, Inc. facilities in Palo Alto, California on November 3, 1999, and they were found to be in compliance with the Device GMP Regulations.

CDRH issued an approval order on June 13, 2000.

XIV. APPROVAL SPECIFICATIONS:

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.